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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,547	10/26/2005	Harvey Kaplan	1658-8/AMK	1415

7590 09/29/2009

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EXAMINER	
AUDET, MAURY A	
ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
09/29/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/524,547	**Applicant(s)** KAPLAN ET AL.	
	Examiner MAURY AUDET	**Art Unit** 1654	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 06 March 2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: _____.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Maury Audet/
Examiner, Art Unit 1654
Full Sign. Auth. Program

Continuation of 11. does NOT place the application in condition for allowance because:
applicant's claimed invention (no amendments), although the arguments have been fully considered, are not found persuasive.
The reasons of record are maintained as to the predictability and thus obviousness of the presently claimed method of making (claims 1-6). In line with the same findings by the International Authority in the related PCT application (3 references cited as "Y" references, latter 2 applied under 35 USC 103 by Examiner), that the present steps are not deemed to present any unexpected results advancing the well known peptide art of vaccum-glycation of protein using a reducing sugar comprising any desired units from 1-50 therefor (claims 1 & 5), inside the claimed pH range (claim 6) and then reducing the same with cyanoborohydride (Tarelli et al.), under known heating ranges/timeframes (claims 3-4, citing Boratynski applying the heating elements for the same process, the heat range/length of time being routinely optimizable parameters).

As noted of record in the Final Rejection, putting the same "under vacuum" is standard practice in this art and art thereon not needed to maintain the rejection. The Examiner merely cited by example Brodsky et al. to the use of vacuum as part of a peptide glycation method. Applicant has asserted Brodsky et al.'s use of vacuum was not in fact 'part' of the lyophilizing/heating steps of glycating the peptide, but rather part of the drying step. The Examiner, upon further review acknowledges that though Brodsky et al. does use a vacuum in the overall process, that he did not in for the purpose of these steps.

Thus, the Examiner, merely by examples, refers Applicant to 3 of his own IDS reference submissions, in the IDS of 5/12/05, #3-#5, p. 2: especially the 1st reference to Taralp, wherein Step 2.8 provides the lyophilization step of heating the product under vacuum at 75 degrees C. for 24 hrs. [Applicant's steps of placing/heating under vacuum, inside both of Applicant's temperature & time ranges; Claims 1, 3-4].

1. TARALP ALPAY ET AL: ("Chemical modification of lyophilized proteins in nonaqueous environments" JOURNAL OF PROTEIN CHEMISTRY, vol. 16, no. 3, 1997, p.183-193, XP009022573):

Step # 2.8. In Vacuo Methylation of cChymotrypsin at LpH 8.0 in Presence of Inhibitors Chymotrypsin (100p~g) was lyophilized directly in the two-chambered reaction vessel from an unbuffered solution (1 ml) at pHS.0, and containing 10 mM indole, 10 mM N-acetyl-L-tryptophan, or no inhibitor. Iodomethane (25/~l) was added, and the vessel was sealed under vacuum and placed in an oven at 75°C for 24 hr.

2. VAKOS HELEN T ET AL. ("In vacuo esterification of carboxyl groups in lyophilized proteins" JOURNAL OF PROTEIN CHEMISTRY, vol. 20. no.6,Aug.2001 ,(2001-08), p.521-531 ,XP009022572)

Step # 2.4.
In vacuo Methylation of Proteins with I~C-lodomethane Proteins (20 rag) ~ere lyophilized without buffier from the fbllowing volumes after adjustmenf of the solution pH with NaOH or HCI: soluble protein (1 mI& insulin (40 ml), Insulin (high purity insulin, mutant recombinant instJlin) and human albumin were dialyzed against 3 >': 4 L distilled water (3500 MWCO dialysis tubing) prior to lyophilization to remove exeipients. In vacuo reactions with [~C]iodomethane t25 btL) were carried out in sealed reaction vessels, which were placed in an oven at 75C fbr 24 hours~ according to the procedure described by Taralp and Kaplan (1997). Reaction vessels were opened and dried by extensive evacuation (typically 2 to 3 hours) to remove any residual reagent and [~3C]methanol side-product,

3. Simons et al. ("Covalent cross-linking of proteins without chemical reagents "PROTEIN SCIENCE, CAMBRIDGE UNIVERSITY PRESS,CAMBRIDGE,GB,voI.11 ,Jun.1,02,p.1558-1564,XP008022328 , which teaches vacuum glycation of peptides was well known in these steps at the time of the invention (2002):

Abstract
A facile method for the formation of zero-length covalem cross-links between protein molecules in the lyophilized state without the use of chemical reagents has been developed. The cross-linking process is perflwmed by simply sealing lyophilized protein under vacuum in a glass vessel and heating at 85';C for 24 h. Under these conditions, approximately one-third of the total protein present becomes cross-linked, and dimer is the major product. Chemical and mass spectroscopic evidence obtained shows that zero-length cross-links are lormed as a result of the condensation of interacting ammonium and carboxytate groups to fl~rm amide bonds between adjacent molecules. For the protein examined in the most detail, RNase A, the cross-linked direct has only one amide cross-link and retains the enzymatic activity of the monomer. The in vacuo cross-linking procedure appears to be general in its applicability because five difl~rent proteins tested gave substantial cross-linking, and co-lyophilization of lysozyme and RNase A also gave a hcterog-eneous covalently cross-linked direct.